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AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph starting on page 2, line 21 and ending on page 3, line 7 with the following amended paragraph:

Several approaches have been taken to design anticoagulant agents. 1) Since one of the major components of thrombus is aggregated platelet-fibrinogen, drugs which prevent the aggregation between platelet and fibrinogen have been designed. A sequence of Arg-Gly-Asp in fibrinogen is responsible to interact with activated platelet so that many peptide or non-peptide based drugs which mimic the tripeptide structure have been developed. Antibodies which block the platelet fibrinogen receptor, glycoprotein IIb-IIIa complex (Gp IIb/IIIa), have also been developed. 2) Tissue factor pathway inhibitor, which inhibits tissue factor and factor VIIa complex, blocks the early stage of coagulation cascade. 3) Protein C is a natural anticoagulant and inactivates factors Va and VIIIa. 4) Currently available drugs which may not be optimized and used in a combination of the existing drugs has been studied. 5) Thrombin plays a central role in coagulation, thrombosis and platelet activation. The direct inhibition of thrombin activity has advantages of independence to co-

factors, efficacy to clot-bound thrombin, less patient-to-patient variability, and low risk of bleeding.

Please replace the paragraph starting on page 4, line 22 and ending on page 5, line 2 with the following amended paragraph:

Investigators have focused on the use of (D-Phe)-Pro-Arg-Pro or its analog in the design of active site inhibitors. The crystal structure of (D-Phe)-Pro-Arg chloromethylketone (PPACK)-thrombin suggested that the (D-Phe)-Pro-Arg-Pro in bivalent inhibitors bind to the thrombin active site in a substrate binding mode, wherein the linkage between residues Arg and X in Arg-X is the scissile peptide bond. The active site inhibitor segment, (D-Phe)-Pro-Arg-Pro, of the bivalent inhibitors is known to be hydrolyzed slowly by thrombin (DiMaio, J., et al., *Supra*; Witting, J.I., et al., *BioChem. J.* **287**, 663-664, 1992). The amino acids (D-Phe)-Pro-Arg comprised in the substrate type inhibitor (D-Phe)-Pro-Arg-Pro bind to the S3, S2 and S1 subsites of thrombin, respectively.

Please replace the paragraph starting on page 8, lines 26 to 34, with the following amended paragraph:

In accordance with the present invention, there is therefore provided a trivalent thrombin inhibitor comprising a S subsite blocking segment, which is connected

to the S' subsite blocking segment, which is connected to the fibrinogen recognition exosite blocking segment. In this invention, the design of the S' subsite blocking segment improved the affinity of the inhibitors by 250–300 [-]fold which is significant and valuable commercially.